Hormones, Nutrition, and Cancer¹

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Summary

The effects of obesity on steroid metabolism in women with breast and uterine cancer have been considered. Obesity may increase plasma estrone by two mechanisms: a higher rate of secretion of the estrone precursor, androstenedione, and a higher rate of conversion of androstenedione to estrone. Obesity may also alter routes of metabolism of androgens and estrogens. The excretion of specific urinary metabolites can therefore be altered by obesity alone. Thus, steroid indices of relative cancer risk or responsiveness must be constructed with due attention to obesity, one of many important variables.

During the planning of this report, I consulted MEDLARS and the indices of CANCER RESEARCH. In the past 3 years, MEDLARS contained only 2 references keyed to the words in the title. Similarly, the indices of CANCER RESEARCH for the past 10 years had few entries under either “diet” or “nutrition.” Thus the intersection of endocrinology and nutrition has not recently been an active point of departure for research or therapy in cancer.

Nevertheless, in human disease, several epidemiological data suggest important influences of nutrition in cancers of the breast and uterine endometrium. The dietary state may influence the rate and route of steroid hormone metabolism. In the former case, the production rate of putative cancer-promoting factors such as estrogens may be altered; in the latter case, the pattern of urinary steroid metabolism may reflect factors other than the production rates of their steroid hormone precursors. I have chosen therefore to discuss primarily those data derived from human studies relating nutrition to hormonal metabolism. It is recognized that there are many data with reference to the experimental animal, showing that malnutrition or starvation can slow the rate of tumor growth. Although the mediation of growth hormone could be involved and although there are experiments in which growth hormone accelerated the appearance of several tumors, the connection between nutrition and tumorigenesis via this mechanism remains tenuous.

Breast Cancer

Estrogen Production Rates. There is circumstantial evidence linking breast and uterine cancer to estrogens. The necessity for estrogens for tumor induction in the rat (8) and mouse (31) has been demonstrated. In man, the diminution of risk for the development of breast cancer afforded by early oophorectomy (13) supports a "permissive" role for estrogens. It then becomes necessary to inquire how nutrition may impinge on estrogen production and the menstrual cycle.

After the menopause, the dominant estrogen in blood is estrone (27, 35). In the post-menopausal woman, only a small fraction of this estrone (about 2%) is secreted by the adrenal, the rest arising by conversion of androstenedione in peripheral tissues (26). The source of this androstenedione is the adrenal cortex (42) and the ovary (22). This means that the estrone production rate and plasma estrone levels depend on the secretion rate of androstenedione and its rate of conversion to estrone.

Aromatization of androstenedione to estrone takes place in the liver (2), fat (38), and brain (32). It is difficult to assess the relative contributions of each tissue, but fat must play an important role. Both estrogen effect (11) and excretion (3) have been related to obesity. The extent of conversion of androstenedione to estrone is higher in obese women than in women of normal body weight (17, 36).

These biochemical phenomena can be related to breast cancer by the observations of DeWaard (9) who has summarized the evidence that obesity or possibly body weight (10) is associated with an increased risk for breast cancer in women over 50 years of age. In a pertinent animal study, there was a marked effect of obesity on the induction of mammary carcinoma in both normal and castrate C3H mice (41). Thus, one may tentatively construct the sequence: obesity → increased conversion of androstenedione to estrone → increased plasma estrone → promoter effects → breast cancer. Clearly, several of the steps in this sequence need experimental validation.

The other mechanism for increased estrone production rates would be an increased secretion of androstenedione or its precursors. To my knowledge, androstenedione production rates have not been correlated with body weight. However, in 1 series (22), plasma androstenedione concentrations were highest in obese women.

Bearing on this problem is the finding that cortisol secretion rates are high in obesity due to an increased clearance rate (30). Furthermore, there is good evidence that dehydroepiandrosterone, a C₁₉ steroid closely related to androstenedione, is secreted synchronously with cortisol (37) and that the adrenocorticotropic hormone increases androstenedione levels (21). It is therefore probable that obesity can increase androstenedione production rates. Thus, increased estrone in obesity may result from 2

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phenomena, higher production and a higher rate of conversion of precursor. It has not been shown yet that this estrogen excess is a factor in the genesis of breast cancer.

Anovulatory Cycles. It has been proposed that anovulatory cycles are related to the development of uterine cancer, the endocrine correlate being the continued unopposed estrogen effect. A similar suggestion has been made with respect to breast cancer (28). Ten years ago, Grattarola (15) presented data showing an association of breast cancer and anovulation, and there are several suggestions that a history of infertility is more common in women with breast cancer than in normal controls. Since obesity is a frequent concomitant of infertility and anovulatory cycles, efforts to relate obesity to breast cancer via this mechanism are warranted. In the only preliminary direct test of this hypothesis, patients with early breast cancer had luteal-phase progesterone levels equal to those of age-matched normal women (40).

Routes of Metabolism. A 2nd area of concern in breast cancer is the effect of nutrition in biochemical epidemiology. In the context of this paper, I refer to those attempts to use measurements of steroid hormone metabolites to distinguish among breast cancer-susceptible groups of women or to predict their responses to therapy. Since the pattern of steroid excretion is determined mainly by hepatic metabolism, factors influencing hepatic enzyme activities would be expected to alter urinary steroids, irrespective of secretion rates. It may therefore be hazardous to infer differences in the endocrine milieu of groups of subjects on the basis of apparently consistent alterations in urinary steroids without considering a variety of environmental and dietary influences.

Bulbrook et al. (1, 5) have proposed that the excretion of etiocholanolone and androsterone, metabolites of adrenal C₁₉ steroids, predict the response to adrenalectomy or hypophysectomy. These measurements have empirical value, but it has been difficult to translate these findings into alterations of adrenal steroid secretion patterns. Bulbrook (4) has catalogued many of the factors affecting urinary androgen metabolites. Nonspecific factors associated with illness have been shown to decrease the conversion of androgens to androsterone and etiocholanolone (43). Starvation markedly decreased the excretion of these steroids without affecting the plasma concentrations of their principal precursor (20). This effect of fasting and starvation has been extensively confirmed recently (29). It is therefore fair to conclude that, unless groups are matched carefully for age, weight, caloric intake, drugs, extent of disease, hepatic function, and perhaps other influences, meaningful comparisons of androgen metabolites cannot be made.

It may well be that urinary metabolites of estrogens pose similar problems. In 1 study, proportionately more estriol was excreted by obese women than by their normal controls (3). The well-known alterations of routes of estrogen metabolism produced by thyroid hormone (14) make it necessary to consider thyroid status carefully, and recently, inanition has been shown to decrease the rate of triiodothyronine formation (6, 34). Since attempts have been made to relate the excretion of estriol conjugates to relative risks for development of breast cancer (23, 24), those factors including nutrition that determine the routes of estrogen metabolism need to be understood and taken into account before attributing other than empirical value to urinary estriol excretion.

Endometrial Cancer

There are many papers calling attention to the association of obesity, infertility, diabetes, and hirsutism with endometrial cancer. In a single study (12), only obesity and infertility could clearly be shown to occur at higher frequency in women with endometrial cancer. However, both diabetes and hirsutism are concomitants of obesity, so that the clinical observations may have validity.

It is perhaps easier to relate the effects of nutrition via the endocrine system to endometrial cancer. We have pointed out the well-known relationships between obesity and anovulatory cycles in young women with endometrial carcinoma. There is a high incidence of irregular menses (33). In other conditions associated with irregular menses, such as the Stein-Leventhal syndrome and functional ovarian tumors, there are also reports of increased frequencies of endometrial cancer (18, 25). Common to these situations is prolonged estrogenic stimulation of the endometrium without gestational effect. The report (7) of endometrial carcinoma occurring in women with gonadal dysgenesis treated for prolonged periods of time with estrogen only, underscores this relationship.

The earlier discussion of the effects of obesity on estrogen production is relevant here. Grodin et al. (16) have found increased estrone production rates in women with endometrial hyperplasia, a probable forerunner of endometrial cancer. Women with endometrial cancer metabolized more androstenedione to estrone than did normal controls (19). Although in neither study was body weight recorded, it seems a pertinent variable. Thus, the association of those factors tending to produce more estrogen and unopposed estrogen effects can be related to endometrial cancer on the one hand and to nutritional status on the other.

Although extremes of nutrition may affect secretion or disposal of polypeptide hormones and possibly other steroid hormones, such as testosterone, no realistic case can be made for imputing a role for nutrition in cancer through these mechanisms. Subtle effects of altered intake and distribution of calories and vitamins are too difficult to discern among the many factors involved in carcinogenesis and tumor progression.

References

3. Brown, J. B., and Strong, J. A. The Effect of Nutritional Status and


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